Quick Update Process for PEN® content

1. Conduct a Literature Search

- Review PEN® Author and Reviewer's Guide: Step 3 Acquire evidence and the PEN® Authors Training Module – Searching PubMed Module
- Document the Search Strategy on the Search Strategy Worksheet

Refer to Example PEN question with Search Strategy at the end of this document.

2. Hierarchical Literature Retrieval to identify literature

- Only incorporate high quality secondary research (e.g. systematic reviews [SRs], guidelines that used a SR process) or high quality / impactful primary research (i.e. high quality work that could affect practice recommendation). Hierarchical literature approach:
  a. If more than 1 SR is identified, pick only one if it addresses all important outcomes
     - Consider: most recent, highest quality and SR that most closely represents PICO
     - Meta-analyses are preferred over narrative summary of results
  b. If no high quality secondary research, a recent narrative review can be used to summarize primary research. Such a review should include a search strategy and be balanced and objective.
  c. Include high quality / impactful primary study(s) only if:
     - it is more recent than the SR
     - it reports an important outcome not included in the SR
     - no review with search strategy is available
  d. Use Search Strategy to document reasons for excluding other reviews / studies that were identified using the hierarchical literature approach
     - PubMed Clinical Queries can help identify systematic reviews: http://www.ncbi.nlm.nih.gov/pubmed/clinical

3. Consider International Recommendations

- Relevant international and national guidelines should be incorporated into evidence statements (applicable to all of our partner countries – Australia, Canada and the United Kingdom). This should include their recommendation and a description of the level of evidence used to develop their recommendation.
  - Government guidelines: NHMRC (Australia), NICE (UK) and Health Canada
  - Clinical practice guidelines from national professional associations: Australian, Canadian and/or UK/European associations (e.g. cardiology, diabetes, gastroenterology, nephrology etc.)
  - TRIP database can help identify guidelines and reviews: https://www.tripdatabase.com/

4. Decide how many Key Practice Points are needed to answer the Question

- For some practice questions, it may be helpful to parcel the research into smaller sections by subtopic. Each subtopic is considered a separate Key Practice Point (KPP) and is treated separately (i.e. each has its own Evidence, Comments, Rationale, Recommendation, Evidence Summary and Remarks sections).
- Multiple KPPs for the same question are derived from the evidence available and created at the discretion of the author. In the past, multiple KPPs have been used to separate evidence by intervention, key nutrient, or outcome, among others. Some examples of questions with multiple KPPs include:
  - Q: What effect do tropical oils (palm oil and coconut oil) have on blood lipids? (by intervention): http://www.pennutrition.com/KnowledgePathway.aspx?kpid=2878&pqcatid=146&pqid=2946

- Q: Do dietary supplements reduce the symptoms of premenstrual syndrome (PMS)? (by dietary supplement) http://www.pennutrition.com/KnowledgePathway.aspx?kpid=2814&pqcatid=146&pqid=732
- Q: Does educating consumers on how to use nutrition facts/information panels increase their use and/or change dietary behaviours? (by outcome) http://www.pennutrition.com/KnowledgePathway.aspx?kpid=1583&pqcatid=146&pqid=26906

5. **Writing the Evidence Section –** This section is comprised of a lettered list. Each lettered point is known as an 'Evidence Statement' and describes a single article in a concise and clear format.
   - For all studies, focus on reporting relevant, patient important outcomes (e.g. mortality, morbidity, functional status, quality of life) rather than every reported outcome. Use surrogate outcomes (e.g. biomarkers, bone density) only if no information is available on patient important outcomes.
     - Refer to International Consortium of Health Outcomes: http://www.ichom.org/medical-conditions/
   - For systematic reviews, note the date of the search, provide a brief description of the question addressed, number and type of articles and participants included (e.g. 12 RCTs (n=375 adults)), then intervention/comparison and outcomes.
   - For primary studies, provide a brief description of population, intervention and results. Detailed inclusion / exclusion criteria does not generally need to be reported. Methods can be incorporated into results (e.g. body fat as assessed by DEXA decreased by 12%)
   - Quality assessment / critical appraisal of the studies should be described in the evidence statement, which will ultimately inform the Grade of Evidence.

6. **Comments and Rationale** – Include any comments (e.g. additional details related to the evidence) and rationale (e.g. proposed mechanism of action) if relevant. These sections are referenced and will help inform the Remarks.

7. **Key Practice Points** (KPPs) – In many ways, KPPs may be considered the 'abstract' of the Evidence, Comments & Rationale sections. They should be written in user-friendly language for dietitians. They should succinctly summarize the evidence statements and include a practice recommendation if possible. Include the following:
   - **Recommendation** – 1 or 2 sentence take-home message. Include a practice recommendation (e.g. no recommendation, recommendation for or against an intervention) if feasible. This is not graded as it is based on the graded evidence (and there may be different grades in the evidence).
     - Country-specific recommendations from clinical practice guidelines or health government agency can be included in the recommendation if it is not reflected in the overall PEN recommendation (E.g. https://www.pennutrition.com/KnowledgePathway.aspx?kpid=2814&pqcatid=146&pqid=732)
   - **Evidence Summary** – a succinct summary (include the size of the effect where possible) and critical appraisal of the Evidence section. Individual statements are graded according to PEN Evidence Grading Checklist
   - **Remarks** (optional) can include:
     - context for the topic (e.g. from Rationale or Comments sections of the question)
     - implementation considerations (e.g. safety, risk/benefit ratio, convenience and burden, costs, nutrient information, patients' value and preferences, health status, co-morbidities, lifestyle culture, etc.)
     - considerations related to subgroups, monitoring and evaluation, need for future research

8. **References –** Use the accepted PEN format. This is easily done by copying and pasting the PubMed reference and URL into your word document and rearranging the order. If reference citation software is used, select 'National Library of Medicine' as the citation style and then add the PubMed URL.

9. **Sending Content for Review**
    a. The following types of updates can generally be sent to the Editor without requiring review (indicate to the Editor what type of update):
        - New evidence added that supports current recommendations
        - New evidence added that supports current recommendations and has resulted in a change in the grade – **this should be checked with an Evidence Analyst for confirmation that it does not require review.**
        - Reviewed and no new evidence identified that changes current recommendations
    b. The following type of update generally requires external review
        - New evidence added that resulted in change to recommendations
    c. When no external reviewers can be identified after an acceptable period of time, an EA will be asked to review content
    d. To reduce reviewer burden and help content move through the update process faster, questions can be submitted through PCMS when several PQs are done instead of waiting until the entire KP is updated.

EXAMPLE of a PEN QUESTION with Search Strategy

Q: What is the clinical effectiveness of the ketogenic diet on weight loss and cardiovascular risk factors in adults with overweight/obesity?

Keywords: body weight high density lipoprotein cholesterol low HDL-C LDL-C triglyceride blood pressure insulin HbA1c glucose low fat carbohydrate diet composition ketogenic diet keto ketones ketosis diet composition ketogenic keto ketones bodies ketosis fad ketogenesis ketosis low carb low-carb very carbohydrate CHO high fat high-fat protein

Search Strategy

Key Practice Point

Recommendation

A very low carbohydrate (20-50 g/day, <10% energy from carbohydrate) ketogenic diet does not result in a clinically important weight loss at one year compared to a low fat diet. The ketogenic diet does improve HDL-C and triglyceride levels compared to a low fat diet; however, LDL-C levels also increase. Adverse effects of the diet have not been well reported. Given the major impact of the ketogenic diet on food choices and the challenges in long-term adherence to the diet, dietitians should discuss with their clients whether the modest long-term effect on weight loss outweighs the disadvantages.

Evidence Summary

Results of a systematic review of 13 RCTs (n=1577) identified that adults with overweight/obesity assigned to a ketogenic diet (<50 g/day carbohydrate or <10% energy from carbohydrate) demonstrated modest greater weight loss at one year compared to a low fat diet (weighted mean difference (WMD), -0.9 kg). The ketogenic diet also achieved greater reductions in serum triglyceride levels (WMD, -0.18 mmol/L) and greater increases in both high density lipoprotein cholesterol (HDL-C) (WMD, 0.09 mmol/L) and low density lipoprotein cholesterol (LDL-C) (WMD, 0.12 mmol/L) concentrations. No overall benefits on blood pressure, insulin sensitivity or A1C were observed. Results are limited by studies with high dropout rates and poor long-term adherence to the ketogenic diet.
{grade_b}

A more recent RCT that compared a healthy low carbohydrate diet (<20 g/day ketogenic diet for two months that transitioned to a low carbohydrate diet over one year) to a healthy low fat diet in individuals with overweight/obesity found that after 12 months there were no differences in weight loss, blood pressure, insulin or blood glucose levels. The ketogenic/low carbohydrate diet achieved greater reductions in triglyceride levels (-14% difference) and greater increases in both HDL-C (5% difference) and LDL-C (5% difference) compared to the low fat diet. The presence of metabolic syndrome was not different between groups.
{grade_b}

In the included trials, adverse effects were either not reported or there were no adverse effects compared to a low fat diet. There are no long-term studies examining adverse effects in participants closely adhering to the ketogenic diet.
{grade_c}

Grade of Evidence: B & C

Remarks

The ketogenic diet (KD) used in these trials comprised of 20-50 g/day carbohydrate or <10% of energy from digestive (net) carbohydrate. In most cases there was good adherence to the diet in the short term. However long-term adherence to the diet was identified as a challenge: at 12 months, participants were generally consuming a low or moderate carbohydrate diet (30-45% of energy from carbohydrate).

The nutritional adequacy of the KD will depend on its overall composition and the nutrient sources. See Additional Content: Diet Composition: Ketogenic Diet Background.

Adverse effects of the KD were not well reported in the included trials. Side-effects of a KD have been reported, including constipation, diarrhea, headache, halitosis, muscle cramps, general weakness and rash.

Evidence

a. A systematic review and meta-analysis (searched to 2012) examined the effect of a very low carbohydrate ketogenic diet (KD) (<50 g/day carbohydrate or <10% energy from carbohydrate) compared to a low fat diet (<30% energy from fat) on weight loss (primary outcome) and blood pressure, lipid levels and glycemia (secondary outcomes) in adults with overweight and obesity (1). A total of 13 RCTs (n=1577 adults, mean age range: 40 to 60 years) were included that followed participants for 12 to 24 months (median=12 months). Participants in the studies had a mean BMI ranging from 32 to 43 kg/m2 and were generally healthy (n=6 trials included participants with no risk factors), or with a cardiovascular risk factor (n=4 trials) or type 2 diabetes (n=3 trials). Nine of the 13 trials were assessed at low risk of bias; however, results are limited by high drop out rates (average 37% dropout; range=13-84%) and there was poor adherence to the KD assessed at 12 to 24 months follow up as measured by dietary assessment (range=36-190 g/day carbohydrate (n=3 trials), 33-47% of energy from carbohydrate (n=6 trials) or not reported (n=4 trials)). Overall results for these outcomes at 12 months:

   - For body weight, the KD groups reported modestly greater weight loss than the low fat diet (WMD, -0.91 kg; 95% CI, -1.65 to -0.17, *P*=0.02). There was no evidence of publication bias. Although the weight loss was significant, the authors' comment that the weight loss differences between groups were not clinically important as it represented only 1% of initial body weight.
   - For blood pressure (BP), results from 11 trials (n=1298 participants) showed no differences between KD and low fat diet for systolic BP (WMD -1.47 mmHg; 95%CI, -3.44 to 0.50, *P*=0.14); however, the KD resulted in greater reductions diastolic BP than the low fat diet (WMD, -1.43 mmHg; 95%CI, -2.49 to -0.37, *P*=0.008). Results for diastolic BP are limited by evidence of publication bias (evaluated by Egger's test).
   - For blood lipids, results from 12 trials (n=1258 patients) identified that the KD compared to the low fat diet produced greater reductions in serum triglyceride levels (WMD, -0.18 mmol/L; 95%CI, -0.27 to -0.08, *P*<0.001) and greater increases in both HDL-C (WMD, 0.09 mmol/L; 95%CI, 0.06 to 0.12, *P*<0.001) and LDL-C (WMD, 0.12 mmol/L; 95%CI, 0.04 to 0.2, *P*=0.002) concentrations. In subgroup analysis, meta-regression analyses showed that studies with 24-month follow up significantly affected the results for triglycerides and HDL-C. No evidence of publication bias was evident for any of the blood lipid outcomes.
   - For insulin sensitivity, no significant benefits of the KD compared to the low fat diet were reported (n=6 trials, 584 participants: WMD, -5.52 pmol/L; 95%CI, -13.62 to 2.57, *P*=0.18). Similarly, no effects on A1C were observed (n=4 studies, 319 patients: -0.24%; 95%CI, -0.55 to 0.06, *P*=0.12).
   - The authors of the review did not report any side-effects of the diets.

b. Published after the aforementioned systematic review (1) the DIETFITS RCT examined the effect of a 12-month healthy low carbohydrate diet (starting with a two-month KD diet) to a healthy low fat diet on weight change (primary outcome) and blood pressure, lipid levels and glycemic control (secondary outcomes) in adults with overweight/obesity (2). A total of 609 participants (mean age 40 years, 57% women, mean BMI 33 kg/m2) were included; none had diabetes but 33% had controlled metabolic syndrome or controlled hypertension. Participants were instructed to follow a KD (20 g/day digestive (net) carbohydrate) or low fat (20 g/day total fat) for two months, then add carbohydrate or fat (5-15 g/day) back into their diet on a weekly basis until they could maintain the diet long term. Both groups received instruction to follow healthy eating patterns (e.g. high intake of vegetables, whole foods and minimally processed foods). The intervention was delivered by health educators in 22 small group sessions over 12 months. At the end of 12 months, data was available for 79% of participants in both groups, but all participants were included in the analysis (i.e. intention to treat analysis). Analysis of dietary intake

(by 3 x 24-hour recalls) showed that both groups had reduced energy intake compared to baseline (~-400-500 kcal/day). Average intake on the low carbohydrate diet was: 30% carb, 45% fat, 23% protein; the low fat diet was: 48% carb, 29% fat, 21% protein. Compared to baseline, at 12 months:

- For weight loss, both groups achieved similar weight loss (low carbohydrate -6 kg; 95%CI, -6.6 to -5.4 kg; low fat=-5.3 kg; 95%CI, -5.9 to -4.7 kg), which was not significantly different (mean between group difference (MD), -0.7 kg; 95%CI, 0.2 to -1.6 kg).
- For BP, both groups lowered systolic and diastolic BP (low carbohydrate=-3.72/-2.64; low fat= -3.18 /-1.94 mmHg) with no difference between groups.
- For lipid levels, both groups decreased serum triglyceride levels with 14% greater reduction in the low carbohydrate group than the low fat diet group (MD, -0.20 mmol/L; 95%CI, -0.33 to -0.09). Both groups increased HDL-C, with 5% greater increase in the low carbohydrate compared to the low fat group (MD, 0.06 mmol/L; 95%CI, 0.03 to 0.86). For LDL-C, the low carbohydrate group showed 5% greater increase compared to the low fat group (MD, 0.15 mmol/L; 95%CI, 0.05 to 0.24).
- For insulin (blood concentration at 30 minutes after oral glucose tolerance test) and blood glucose, both groups improved to a similar extent.
- The decrease in the prevalence of metabolic syndrome was comparable in both groups.
- A total of seven serious adverse events (e.g. kidney stones, diverticulitis) and 11 adverse events were reported during the trial. These adverse events were evenly distributed between the two groups.

Comments

Although adverse effects were not reported (1) or identified (2) in the included studies, a narrative review (3) identified minor adverse effects in a study comparing the ketogenic diet to a low fat diet: constipation, diarrhea, headache, halitosis, muscle cramps, general weakness and rash. Other noted risks from case reports were impaired mood, ketoacidosis, acute pancreatitis and exacerbation of a panic disorder.

References

1. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr. 2013 Oct;110(7):1178-87. doi: 10.1017/S0007114513000548. Epub 2013 May 7. Abstract available from: https://www.ncbi.nlm.nih.gov/pubmed/23651522
2. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. JAMA. 2018 Feb 20;319(7):667-79. doi: 10.1001/jama.2018.0245. Abstract available from: https://www.ncbi.nlm.nih.gov/pubmed/29466592
3. Sumithran P, Proietto J. Ketogenic diets for weight loss: a review of their principles, safety and efficacy. Obes Res Clin Pract. 2008 Mar;2(1):I-II. doi: 10.1016/j.orcp.2007.11.003. Abstract available from: https://www.ncbi.nlm.nih.gov/pubmed/24351673

Search Strategy

PEN Question: What is the clinical effectiveness of the ketogenic diet on weight loss and cardiovascular risk factors in adults with overweight/obesity?

SEARCH TERMS

MeSH Terms

Diet, ketogenic
Diet, carbohydrate-restricted
Diet, high-protein low-carbohydrate
Overweight
Obesity
Body weight
Weight loss
Cardiovascular disease
Metabolic syndrome
Blood pressure
Cholesterol, HDL
Cholesterol, LDL
Triglycerides
Blood glucose
Glycated hemoglobin A
Insulin

Text words

Ketogenic diet
Body weight

Databases and Grey Literature Sources (e.g. international guidelines) SEARCHED

PubMed
TRIP

Reasons for excluding reviews or studies identified using a hierarchical literature search

Clinical trials with short follow-up (<12 months) and small numbers of total participants (<40)

DATE Search Completed: July 1, 2018

Search Limits (e.g. date, language):
2012-2018, English language